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PIPERIDINE SYNTHESIS

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RESEARCH DIRECTORATE

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ARMAMENT
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CHEMICAL COMMAND

Aberdeen Proving Ground, Maryland 21010-5423

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Methods of synthesizing piperidines have been reviewed. The older reviews are cited; however, much of the review is occupied with the research of the last 3 years.

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PREFACE

The work described in this report was authorized under Project No. 10161102A71A, Research in CW/CB Defense. This work was started in April 1992 and completed in June 1992.

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Acknowledgments

Successful completion of this project would have been impossible without the assistance of the dedicated staff of the CRDEC Technical Library. Particularly helpful were Corky Smith and Patsy D'Eramo.

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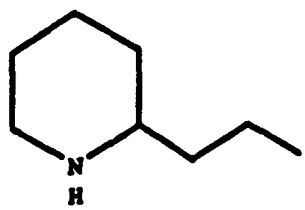
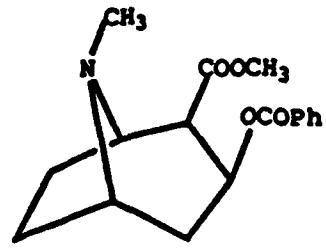
PIPERIDINE SYNTHESIS

1. INTRODUCTION

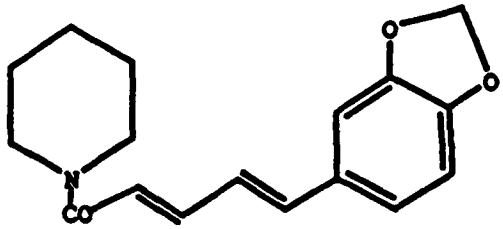
Given the prevalence of the strain-free cyclohexane system in nature, it is not surprising that its heterocyclic relative, azacyclohexane, or piperidine, is a common structural unit in natural products. The piperidine ring system is found in a large number of alkaloids having a diverse spectrum of physiological activity. Structurally simple α-coniine, found in hemlock, is a powerful poison. Extraction of the leaves of the coca bush, and further purification produces cocaine, a powerful,



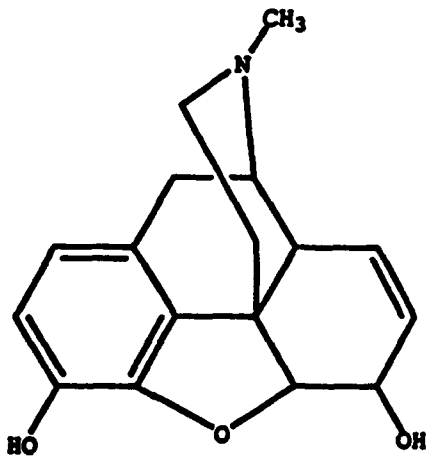
α-coniine



cocaine



piperine



morphine

addictive stimulant. The active principal of black pepper is piperine. The powerful analgesic morphine is derived from the dried latex of the opium poppy. The piperidine ring is found

in alkaloids derived from pomegranate, sedum, lobelia, pine species, papaya, the scent gland of the musk deer and betel nuts.[1]

While we have been provided with an impressive array of physiologically active piperidines, it is tempting and often challenging to design and synthesize molecules that are predicted to have superior properties to those of their natural counterparts. For example, in the realm of analgesics that are derived from morphine, the umbra of respiratory depression accompanies its beneficial effects. One approach to this problem was to assume that unwanted side effects were produced because the dose at which morphine had to be administered for effective analgesia exceeded the threshold for respiratory depression mechanisms. If an extremely potent drug were found, it might be possible to administer it in a dose low enough that those mechanisms leading to respiratory depression would not be triggered. Research at Janssen Pharmaceuticals in Belgium in the 1960's led to the discovery of the drug fentanyl. This relatively simple molecule is almost 300 times more potent than morphine in animal studies. While one side effect, cardiac depression, can be minimized, respiratory depression still must be dealt with at therapeutic doses. Many derivatives of fentanyl have been prepared, some of which are almost 30 times the potency of fentanyl. All appear to retain fentanyl's untoward side effects.

We have been interested for some time in studying the metabolites of fentanyl, as possible analgesics in their own right, and for clues as to how unacceptable side effects might be minimized. As part of this program, the literature has been searched for methods of preparing piperidines, with special emphasis on those substituted at the 3- and 4-positions. This review is a compilation of the best and most recent synthetic methods. Hopefully it will prove useful in leading the researcher to an efficient route for synthesis of a target piperidine.

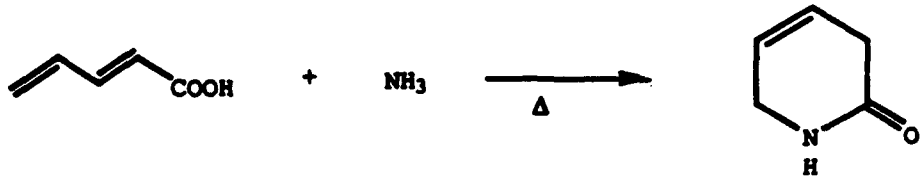
2. SYNTHETIC METHODS[2]

The preparation of piperidine itself is conveniently accomplished by the catalytic hydrogenation of pyridine, most often with a nickel catalyst at 170 - 200°. Other reducing agents are sodium in ethanol or tin in hydrochloric acid.

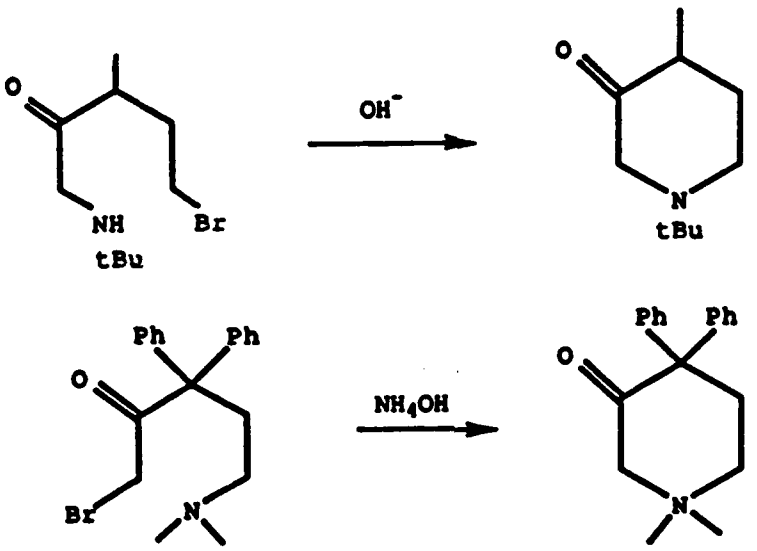
1,5-Dichloropentanes, obtained by treatment of tetrahydropyrans with concentrated hydrochloric acid, can be cyclized to piperidines by treatment with primary amines. 5-Amino-1-haloalkanes, 1,5-diaminopentanes, δ-aminocarbonyl compounds and 5-aminoalkanols are also sources of piperidines.

Piperidones are useful intermediates for the preparation of the subject compounds. 3,4-Substituted 2-piperidones can be reduced to the corresponding piperidines with a variety of reducing agents, eg., $LiAlH_4$ or $NaBH_4$. Substituted 3-piperidones upon reduction are a source of the 3-hydroxy derivatives, while 4-piperidones are frequently employed in the synthesis of fentanyl and its derivatives.

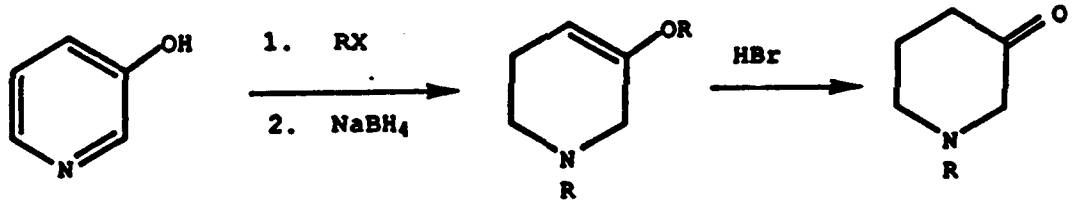
Sundberg and coworkers[3] shook a mixture of vinylacrylic acid, conc. aqueous ammonia and a trace of hydroquinone in a high pressure bomb at 180° for 14 h. A 30% yield of pure 5,6-dihydro-2(1H)-pyridone was obtained.



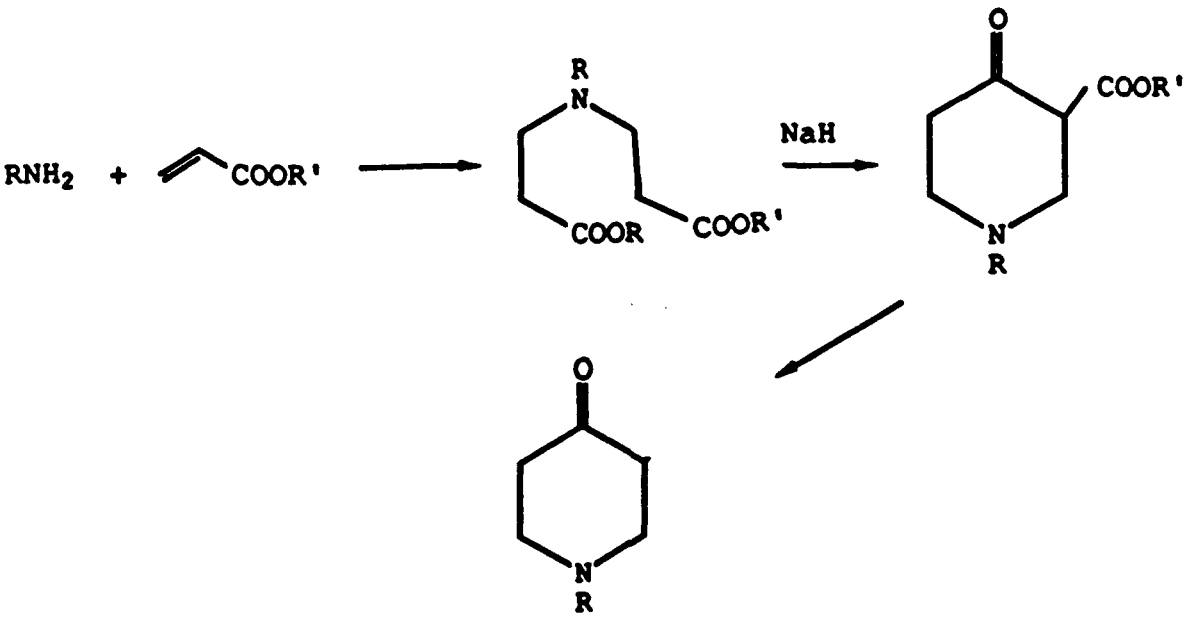
δ-Valerolactams can be prepared by the reductive cyclization of γ-carboalkoxynitriles, γ-carboalkoxyimines (shown below), δ-aminoamides or δ-haloamides.



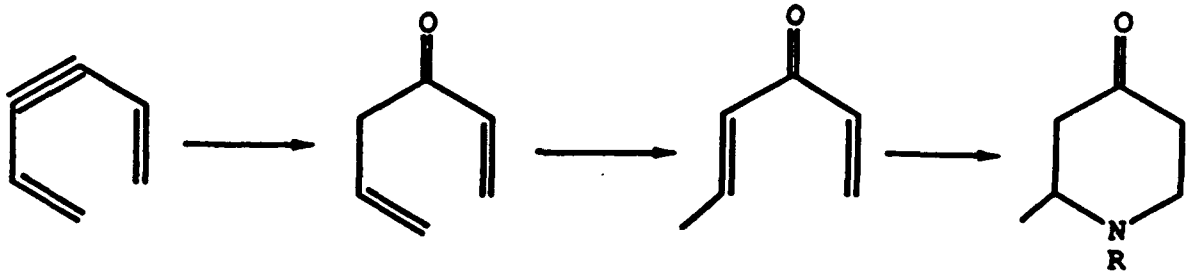
Alkylation of commercially available 3-hydroxypyridine with iodomethane or benzyl chloride followed by sodium borohydride reduction and HBr cleavage of the enol ether is yet another effective route to 3-piperidones.



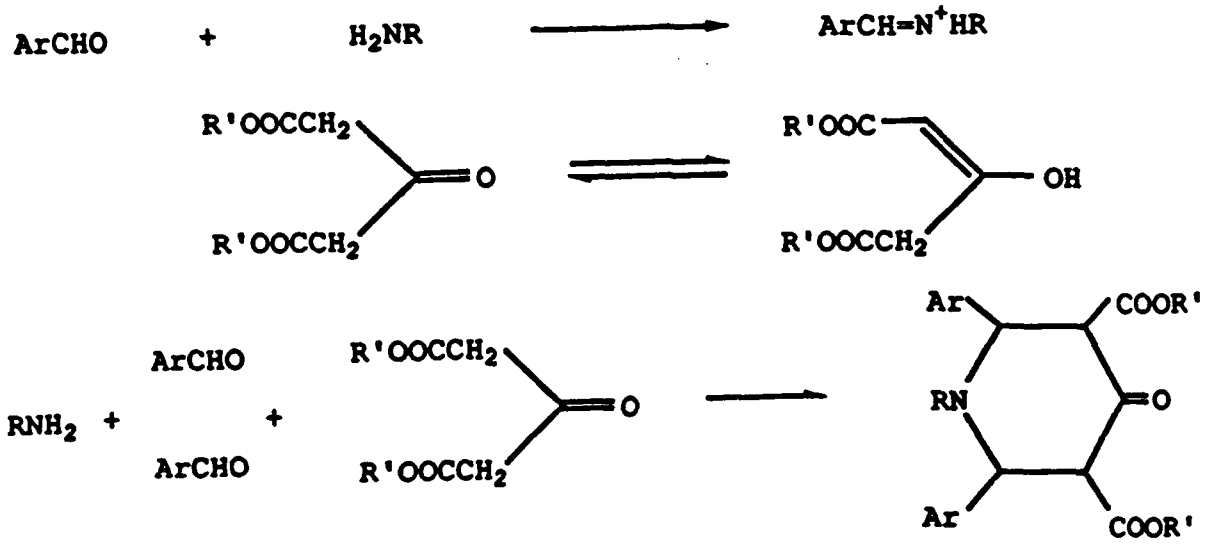
4-Piperidones are most often synthesized by means of the addition of a primary amine to two moles of an alkyl acrylate, followed by the Dieckmann condensation hydrolysis and decarboxylation.



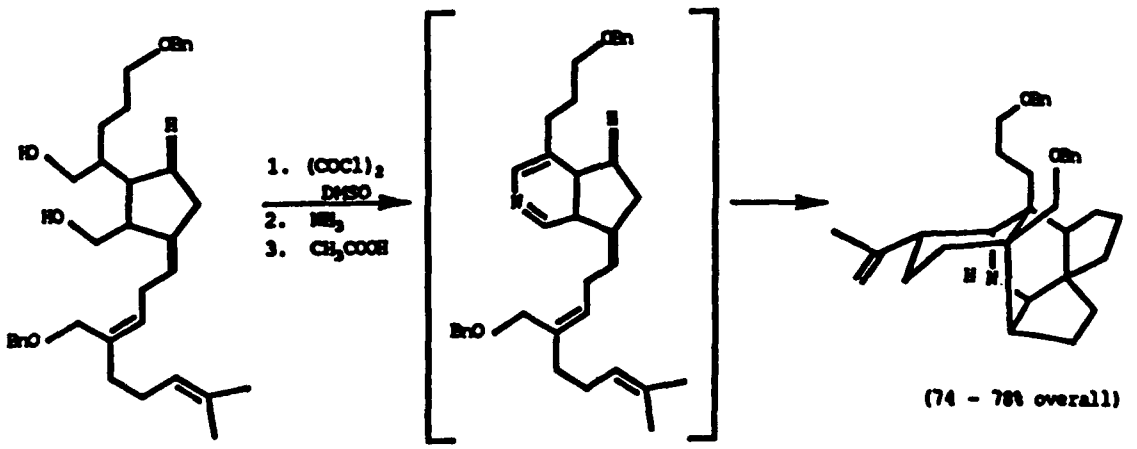
The Nazarov cyclization can be performed on ynedienes obtained from the dehydration of vinyl propargyl alcohols. Chemoselective hydration of the triple bond with sulfuric acid in the presence of Hg(II) followed by double Michael addition to the dienone provided the 4-piperidone.



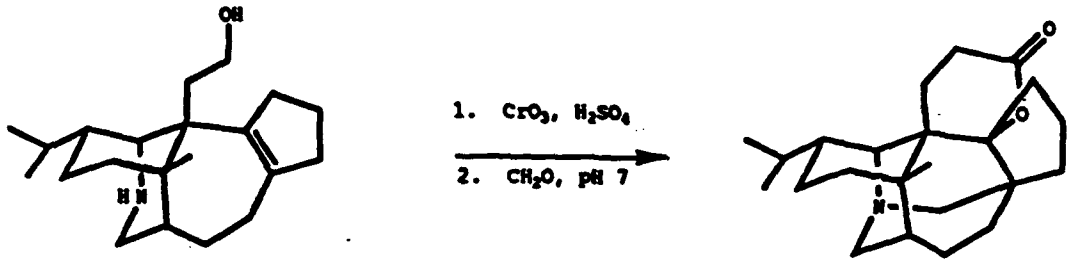
In the Petrenko-Kritschenko reaction, two moles of an aromatic aldehyde are condensed with a primary amine and a dialkyl β-ketocarboxylate in a double Mannich reaction. The initial mechanistic steps and the total reaction are given below.



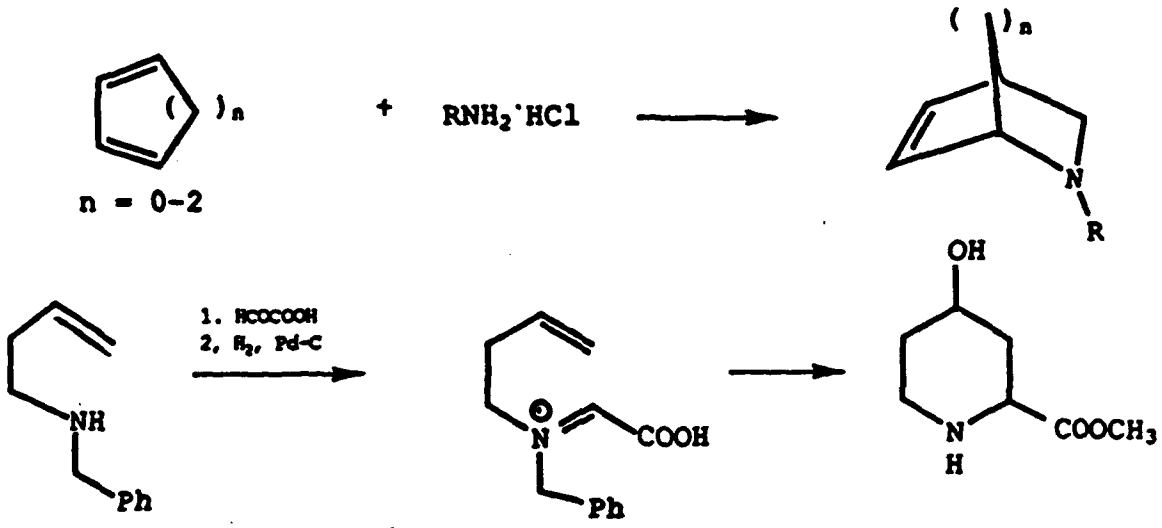
Heathcock[4] has conducted elegant studies on the synthesis of daphniphyllum alkaloids. In the first study, a synchronous inverse electron demand Diels-Alder reaction of a 2-aza-1,3-butadiene obtained by the Swern oxidation of a diol followed by treatment with ammonia and then acetic acid, was exploited for the closure of a second piperidine ring. In another investigation,[5] the



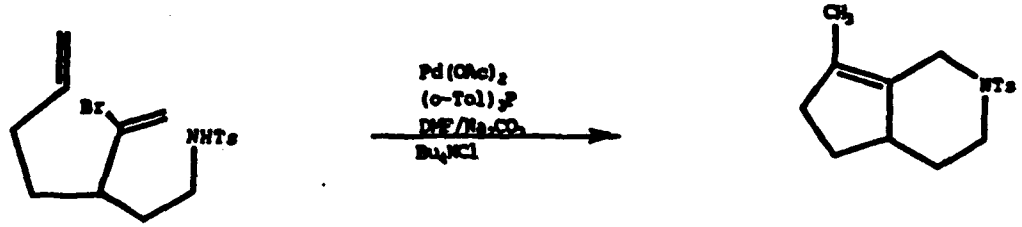
tetracyclic amino alcohol is oxidized to a carboxylic acid. Upon treatment with formaldehyde and adjustment of the pH to 7, iminium ion formation occurs, initiating the addition of the carboxylate function to the double bond, and formation of a second piperidine ring.



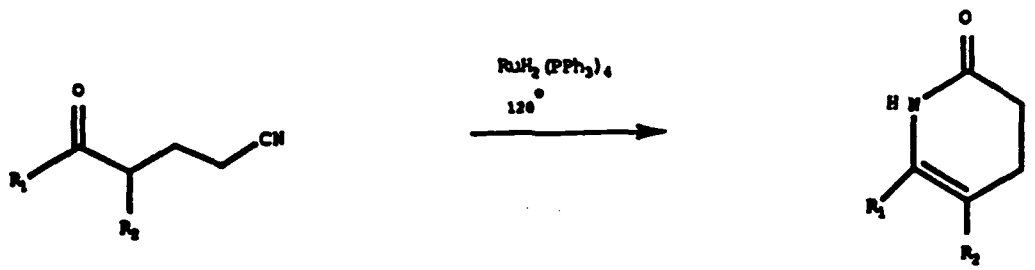
Cycloaddition chemistry has also been recently exploited by Hays[6] who prepared 4-piperidinols via a concerted olefin-iminium ion cyclization by means of an extension of the work of Grieco's group.[7,8]



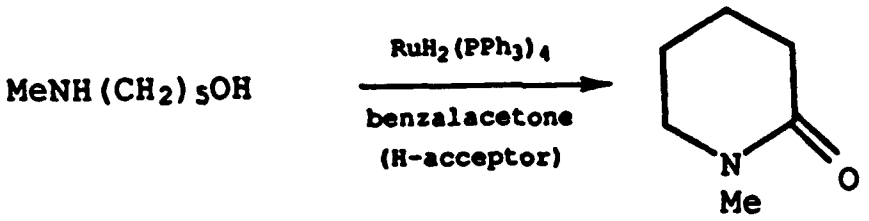
Palladium (II) is an effective catalyst for cyclization chemistry of a bromodiene.[9] A ruthenium catalyst is an effective



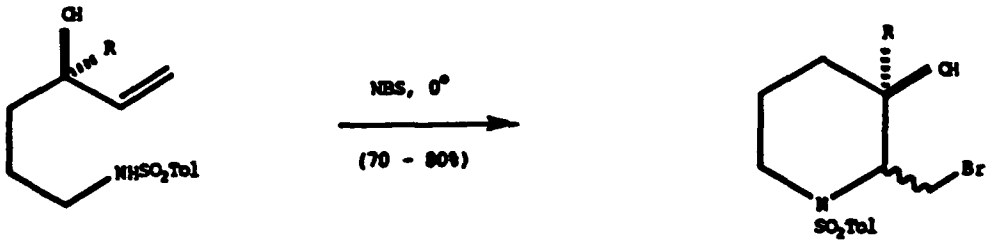
means of cyclizing δ-ketonitriles.[10] Naota and Murahashi[11] found



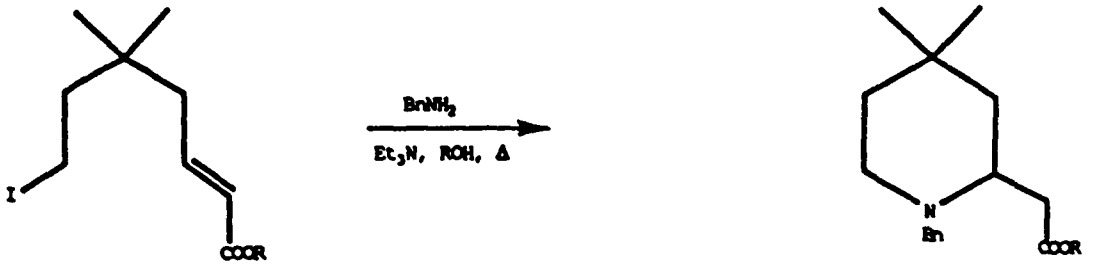
that the same catalyst effected ring formation for 5-amino-1-alkanols, providing a hydrogen acceptor was present.



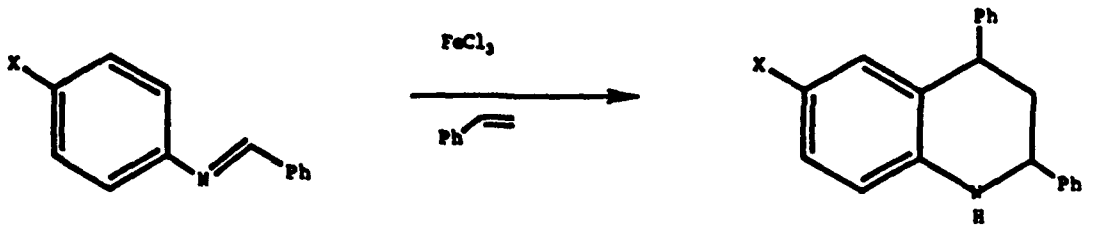
Tamura and coworkers were able to cyclize unsaturated tosylamides with N-bromosuccinimide.[12]



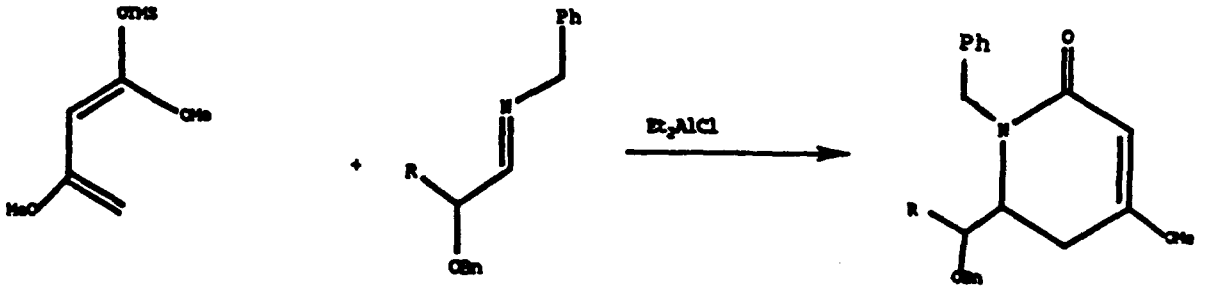
An interesting reaction was reported by Bunce and coworkers.[13] An alkyl 7-iodoacrylate, synthesized from the 5-haloalkene, underwent a Michael addition and an intramolecular nucleophilic displacement reaction when heated in the presence of benzylamine and triethylamine.



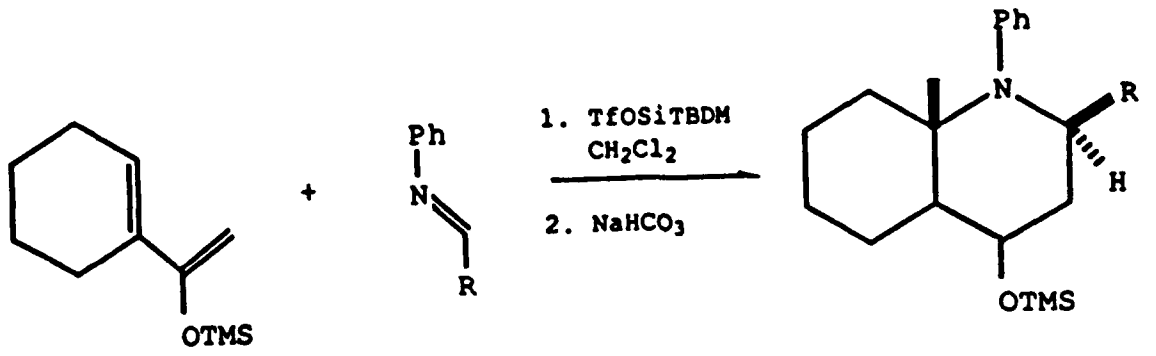
A formal heterocyclic Diels-Alder reaction of 2-aza-1,3-butadiene to styrene occurs in the presence of ferric chloride.[14] The best yield of product is 80% when X is the isocyanide functionality.



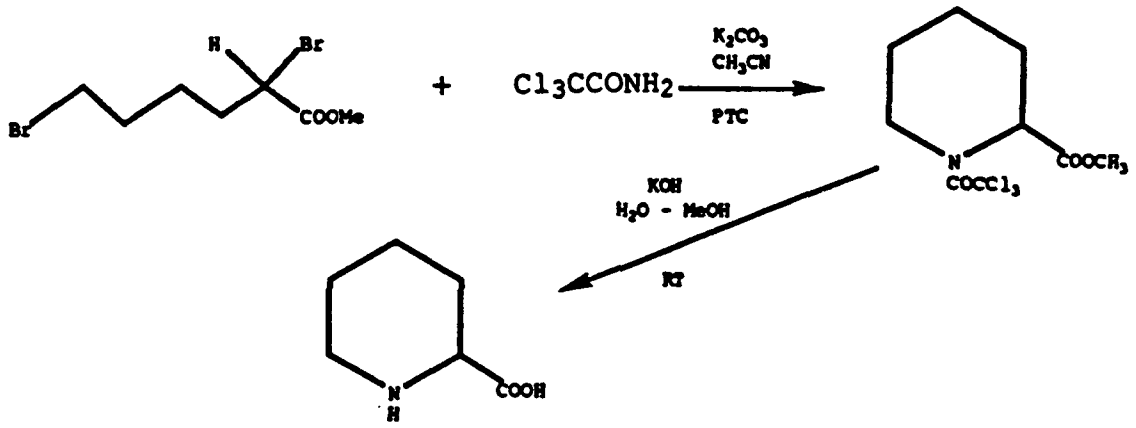
Lewis acid catalysis is an effective means of accomplishing 4 + 2 cycloaddition chemistry between electron-rich dienes and imines.[15,16] Another method for imine cycloaddition employs



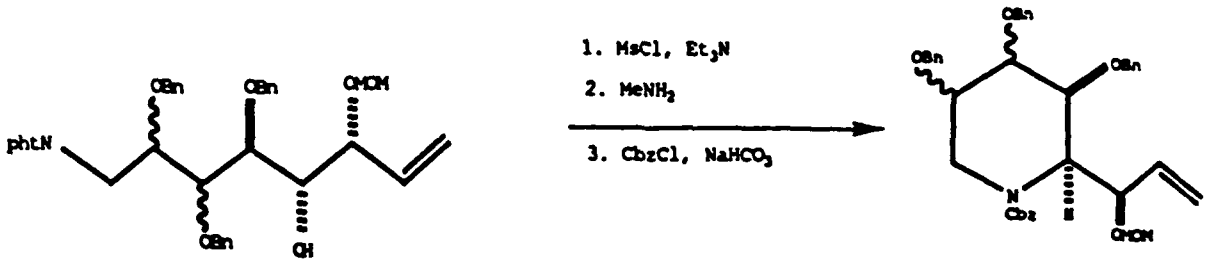
a triflate in methylene chloride.[17]



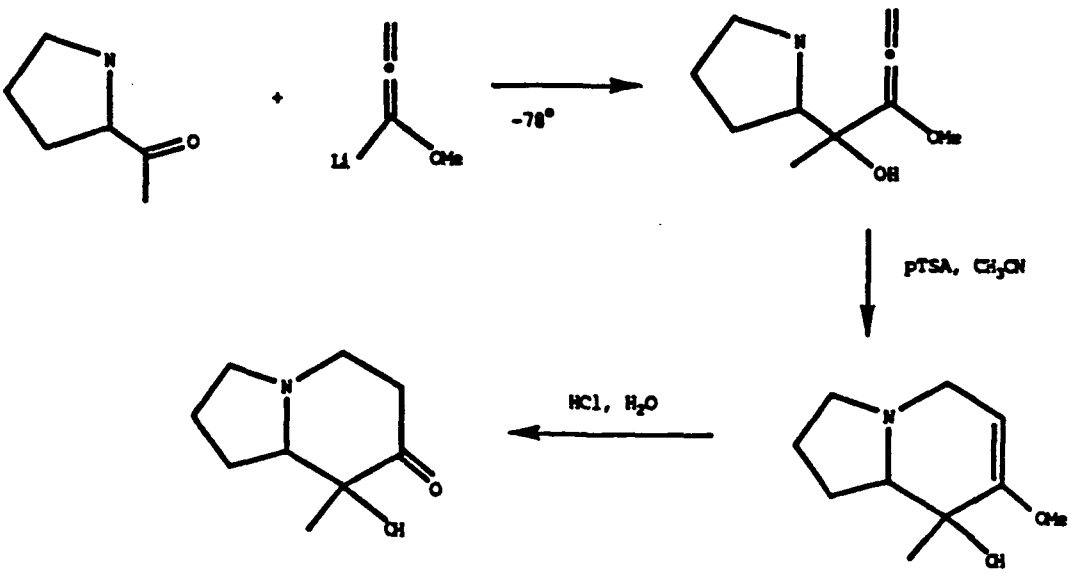
Solid-liquid phase transfer catalysis conditions were utilized to effect the cyclization reaction of the 2,6-dibromocarboxylic ester and trichloroacetamide. Upon hydrolysis, an amino acid is produced.[18]



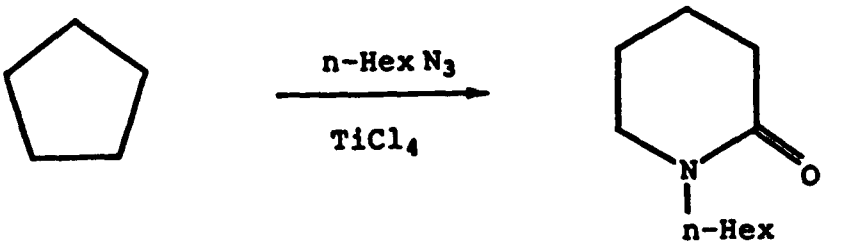
A quadruply protected piperidine may be synthesized as shown below.[19] After preparation of the mesylate, and N-deprotection cyclization occurred in refuxing ethanol. The product is a point of entry for synthesis of several of the stereoisomers of the potent glucosidase I inhibitor, castanospermine, a natural product relevant to the treatment of the HIV-1 virus.



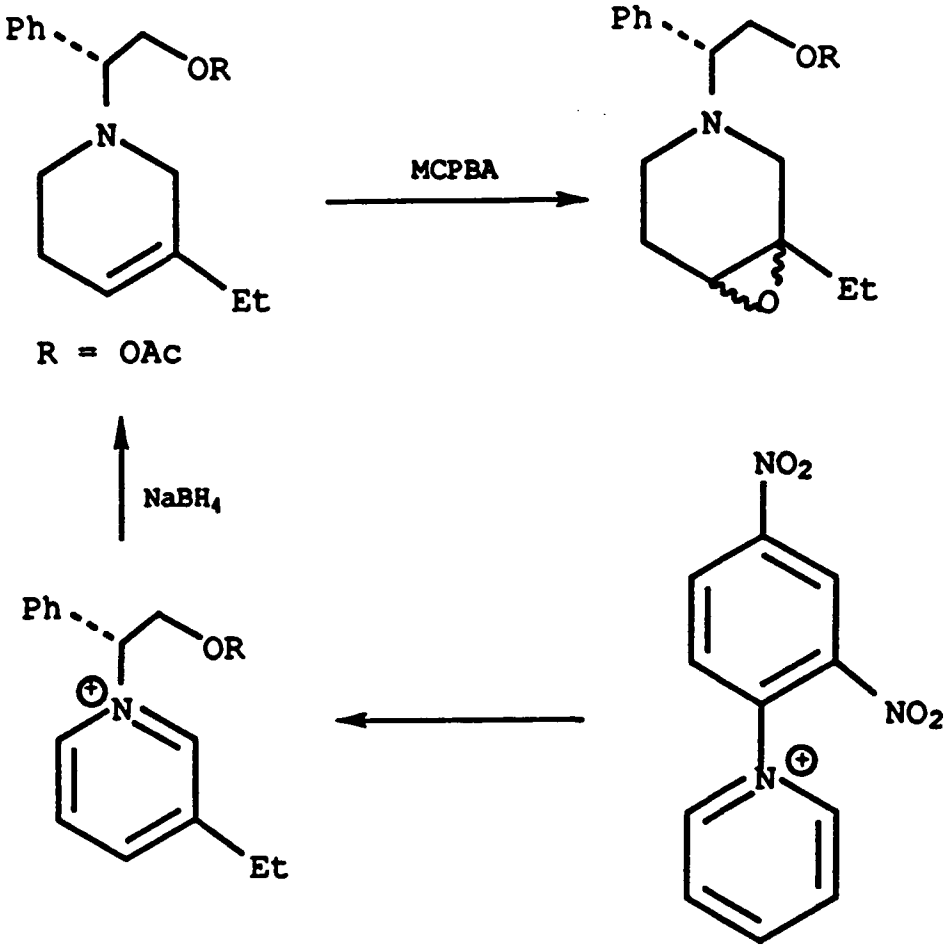
In the presence of p-toluenesulfonic acid the aminoallene smoothly cyclizes to a 4-piperidone precursor.[20]



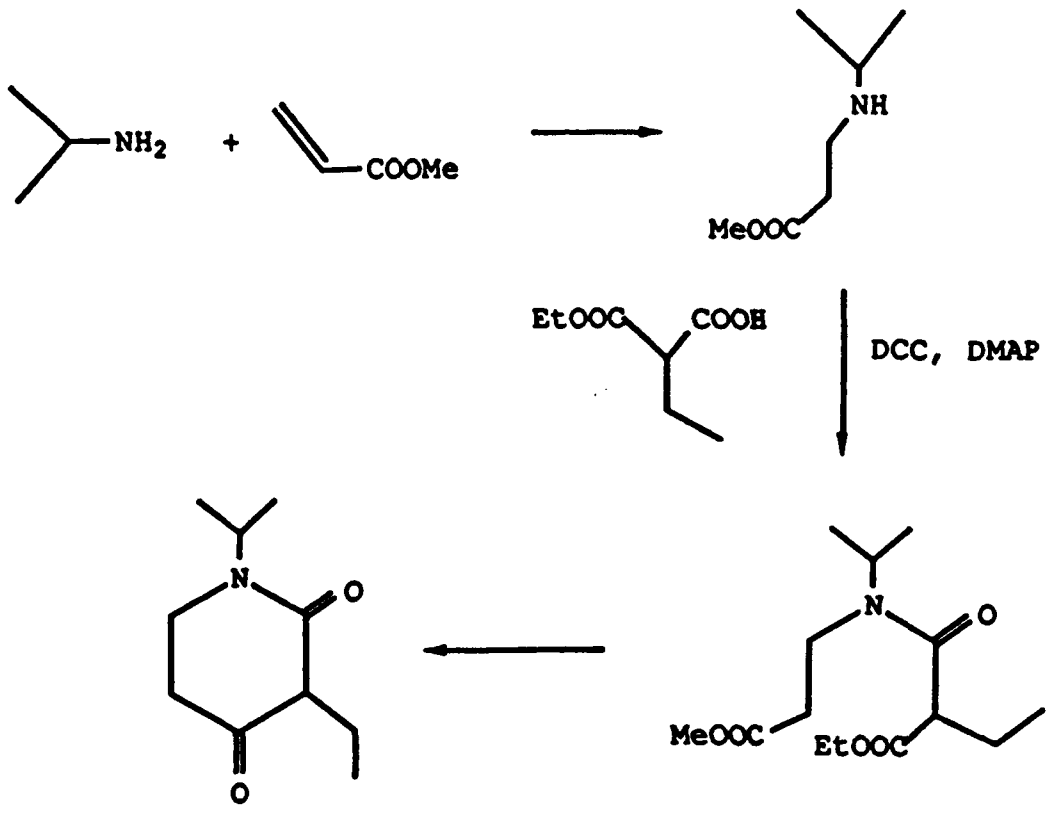
An interesting ring expansion reaction using alkyl azides has been reported.[21] Unfortunately, the yields in reactions resulting in piperidines are disappointing.



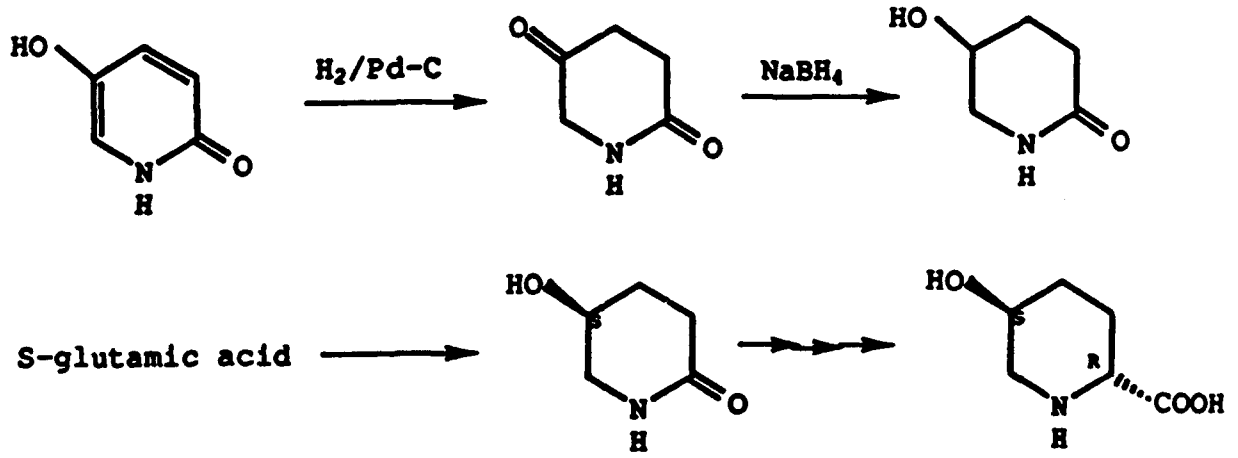
A recent transformation of a pyridinium salt is noteworthy in that epoxidation occurs smoothly in the presence of a tertiary nitrogen.[22] This may be an effective means of preparing 3-hydroxy-4-anilinopiperidines.



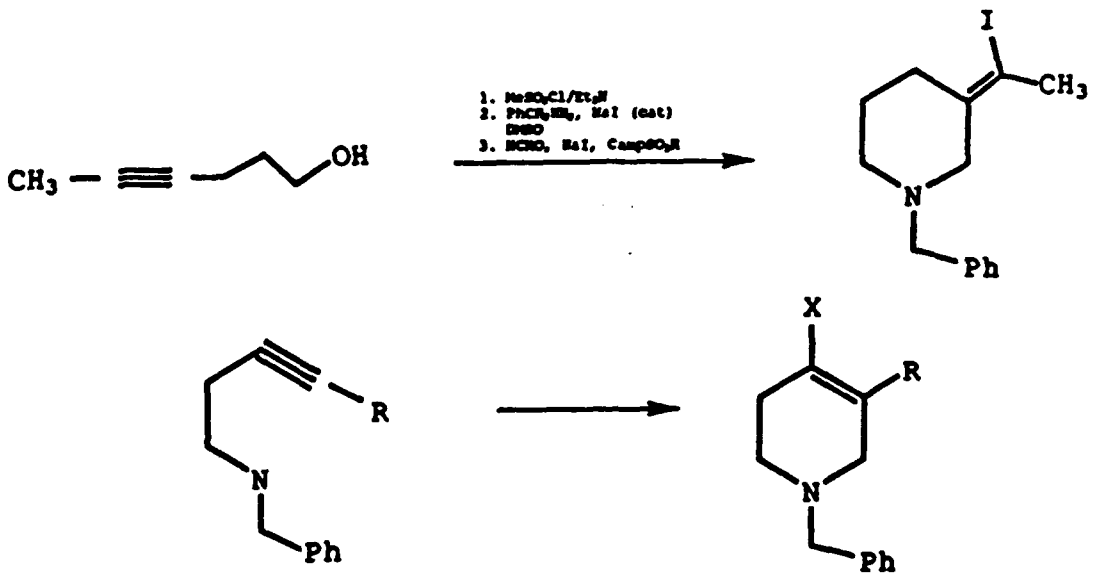
The Dieckmann condensation has recently been used for ring closure in the synthesis of 2,4-diketopiperidines.[23]



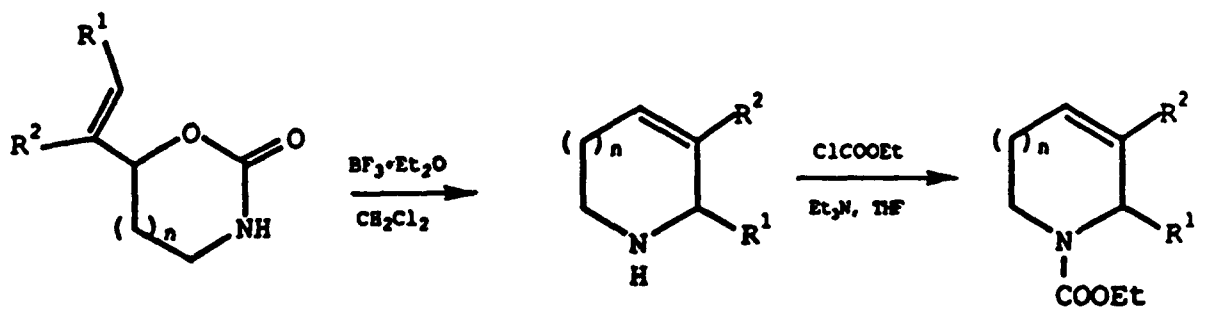
Herdies[24] was able to transform S-glutamic acid to S-5-hydroxy-2-piperidone, which was converted in a series of stereocontrolled reactions into the R-amino acid.[25] This is an extension of earlier work in which 3-hydroxy-2-piperidone is reduced first to the ketoamide, and then to the hydroxyamide.



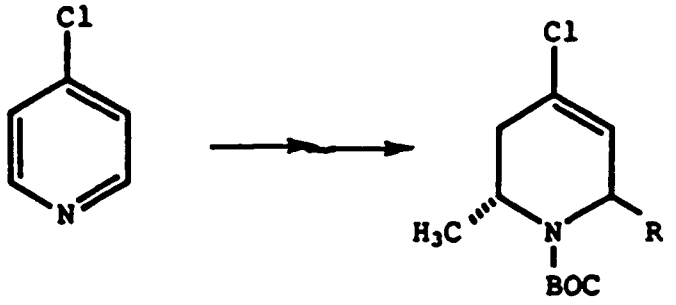
Overman has explored the cyclization chemistry of aminoalkynes.[26]



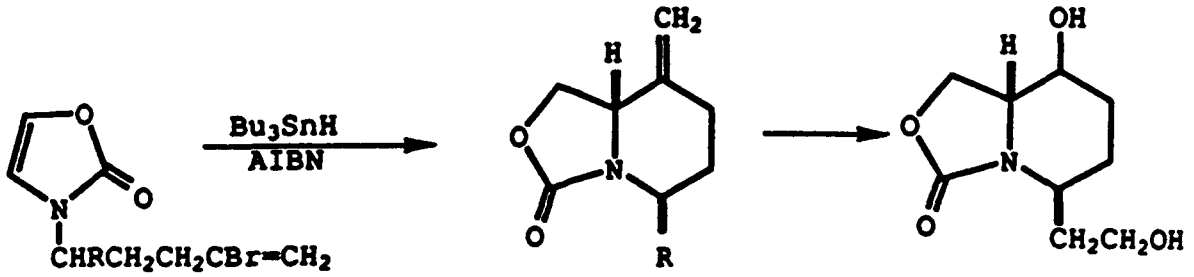
A [3.3] sigmatropic shift[27] has been reported for preparation of 1,2,3,6-tetrahydropyridines, complementing the reduction



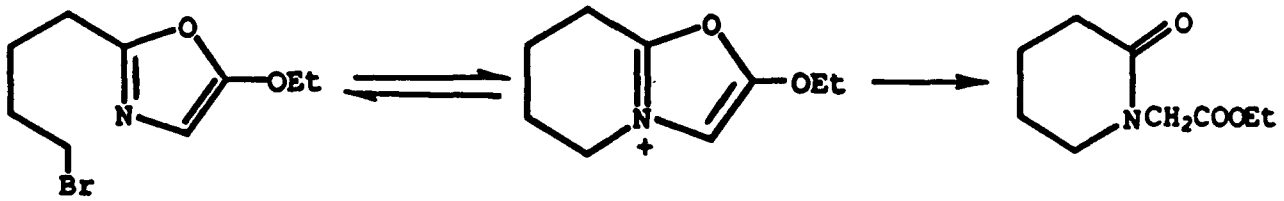
chemistry which continues to be exploited in research projects.[28]



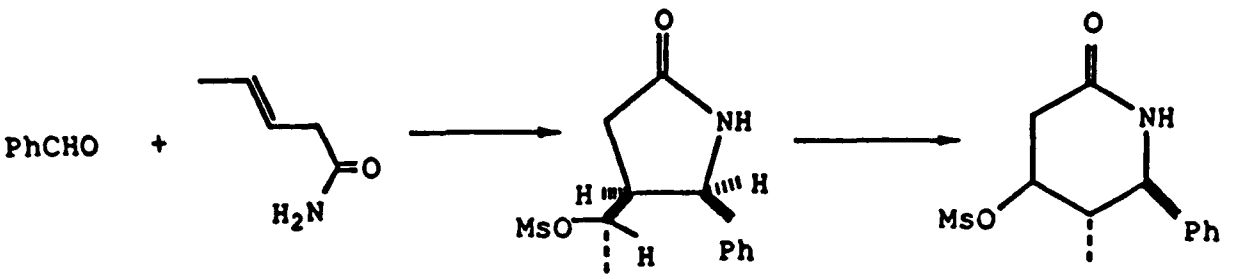
Radical cyclization of a Δ^4-1,3-oxazolin-2-one can be effected with high diastereoselection.[29] Oxidation of the initial product produces a highly functionalized 3-hydroxypiperidine.



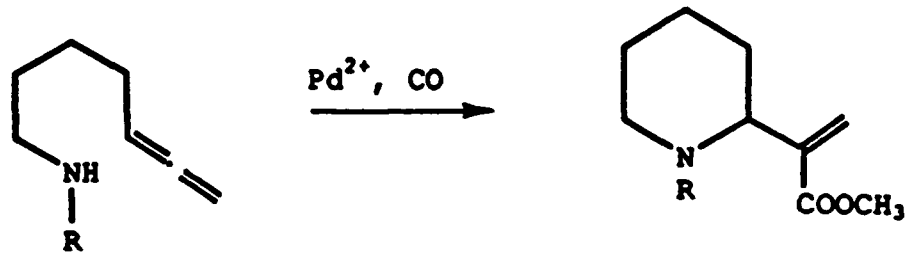
Hassner was able to convert 5-ethoxyoxazoles to 2-piperidinones via the oxazolium salts.[30]



An interesting ring expansion reaction has been reported by Marson.[31] The reaction can be used in stereospecific synthesis.



When allenic amines are treated with carbon monoxide and methanol in the presence of Pd(II) a useful ring closure occurs.[32]



R = H, Bn, SO_2pTol, COOMe

Photochemical amine-enone cyclization routes to piperidines have been summarized by Mariano.[33]

Finally, the collaborative efforts of Padwa's group at Emory and Rodriguez at Clark Atlanta University have resulted in elegant cycloaddition chemistry using 2,3-bis(phenylsulfonyl)-1,3-butadiene with oximes, enamines (and amidines corresponding to enamine equivalents) and ynamines.[34,35]

3. CONCLUSIONS

Due to the importance of the piperidine ring system in natural products and in synthetic compounds with physiological potency, an increasing number of new and versatile syntheses have been reported. It is likely that activity in this area will continue unabated.

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